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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/633,630	08/05/2003	Klaus Giese	39078-0005	6369

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EXAMINER	
CHONG, KIMBERLY	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 10/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/633,630	GIESE ET AL.	
	Examiner	Art Unit	
	Kimberly Chong	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-23,25-27,29 and 31-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-23,25-27,29 and 31-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 07/12/2006 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 01/12/2006 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 07/12/2006, claims 11-23, 25-27, 29 and 31-33 are pending and currently under examination. Applicant has canceled claims 1-10 and 24 and claims 28 and 30 are withdrawn.

New Claim Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 14 and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 14 and 15 recite the limitation "said stretch" in second. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 11-23, 25-27, 29 and 31-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over McSwiggen et al. (cited on PTO Form 892 filed 01/12/2006) in view of Holen et al. (Nucleic Acids Research 04/30/2002).

The instant claim 11 is drawn to a ribonucleic acid molecule comprising a double stranded structure having a first and second strand wherein the first strand comprises a first stretch of contiguous nucleotides and wherein the second strand comprises a second stretch of contiguous nucleotides, wherein said first stretch and/or said second stretch comprises a pattern of a plurality of groups of modified nucleotides having a modification at the 2'-position, wherein each group of modified nucleotides with a stretch is flanked on one or both sides by a flanking group of unmodified or differently modified nucleotides. Claim 11 is further limited wherein each of said groups of modified or flanking nucleotides comprises one to ten nucleotides, wherein the pattern of modified nucleotides of said first stretch is the same as the pattern of modified nucleotides of said second stretch, the pattern of modification of said first stretch aligns or is shifted by one

or more nucleotides with the pattern of modification of said second stretch (claim 12-15), wherein the modification is selected from the group as listed in claim 16, wherein the double stranded structure is blunt ended at one or both ends, wherein at least one of the two strands has an overhang of at least one nucleotide at the 5'-end, wherein the complementarity between said first strand and the target nucleic acid is perfect, wherein the duplex formed between said first strand and the target nucleic acid comprises at least 15 nucleotides and wherein there is one mismatch or two mismatches between said first strand and the target nucleic acid (claims 17-20), wherein the first and second strand are linked by a loop structure wherein the loop structure comprises a non-nucleotide acid polymer or is comprised of a nucleic acid (claims 21-23 and 25-27), wherein said ribonucleic acid is in a pharmaceutical composition and an organism comprising a cell and wherein the length of the double-stranded structure is from about 17 to 21 bases (29, 31-33).

McSwiggen et al. discloses a ribonucleic acid comprising a double stranded structure wherein the first and second strands comprise a first stretch of contiguous nucleotides that are at least partially or perfectly complementary to target molecule (see paragraph 0017 and 0121) and wherein the double stranded structure is between 19-25 nucleotides (see paragraph 0035). McSwiggen et al. further discloses the double stranded structure comprises a plurality of groups of 2'-modified nucleotides, flanked by modified or unmodified nucleotides that consist of one to ten nucleotides and the modification at the 2' position can comprise a methoxy or flouro wherein the two strands are aligned (see Figure 5). McSwiggen et al. teach, in Figure 5, a double stranded

structure comprising a first strand and second strand wherein the first and second strand comprises groups of modified nucleotides at the 2' position. Specifically, SEQ ID NO. 665 comprises a nucleotide sequence of a sense strand comprising nucleotides "cAuGGcuGccAucuGCGccTT" wherein the lower case nucleotides are 2'-O-Methyl modified nucleotides and the upper case are unmodified nucleotides. The above recited sequence comprises a plurality of groups of modified nucleotides at the 2' position wherein the modified groups are flanked by unmodified nucleotides. Further, the above recited sequence comprises a 2'-position modified group that is repeated at least once forming a pattern wherein the pattern is, starting from the 5' end: two 2'-position modified nucleotides i.e. groups, wherein this pattern of modified groups is flanked by an unmodified nucleotide on one side. This pattern is repeated at least five times in the sequence as designated herein by bolded nucleotides: "**cA**uGG**cu**G**cc**A**uc**u**G**CGc**c**TT". Further this pattern, two 2'-position modified nucleotides flanked by an unmodified nucleotide on one side, is the same on the antisense strand of the double stranded structure. McSwiggen et al. teach in Figure 5B, the pattern of modification on the first strand is shifted by one nucleotide relative to the pattern of modification on the second strand. McSwiggen et al. further disclose the modified nucleotide on the first strand is complementary with an unmodified nucleotide on the second strand, the terminal 5' nucleotide of the first strand is modified and the terminal 3' nucleotide of the second strands is a flanking nucleotide and further wherein the modified nucleotide is on the 5' end relative to the flanking unmodified nucleotide (see Figure 5). McSwiggen et al. further disclose the ribonucleic acid first and second strand are linked by a loop

structure wherein the loop structure can be a nucleotide of a non-nucleotide linker (see paragraph 0017 and Figure 6). McSwiggen et al. further disclose a ribonucleic acid in a pharmaceutical composition (see paragraph 00198) and a cell in an organism comprising the ribonucleic acid (see paragraph 0027).

McSwiggen et al. does not teach a dsRNA wherein there is one or two mismatches between said first strand and the target nucleic acid in said dsRNA.

Holen et al. teach dsRNAs containing either one or two mismatches relative to an mRNA (see page 1763, column 1, second paragraph and Figure 6). Holen et al. teach that incorporating mismatches in dsRNAs are desirable to investigate the tolerance of the RNAi system for mismatches in the siRNA relative to the mRNA target. Figure 6 exemplifies the tolerance of RNAi for one or two mutations of the dsRNAs relative to the target mRNA.

It would have been obvious to one of ordinary skill in the art to incorporate mutations of dsRNA relative to a target gene, as taught by Holen et al. into the dsRNA, as taught by McSwiggen et al.

One would have been motivated to incorporate such mutations because Holen et al. expressly teach dsRNA with one or two mismatches relative to the target gene and further one would have been motivated to incorporate such mutations into dsRNA because such mutations would be desirable to investigate the tolerance of the RNAi system for mismatches and would additionally facilitate the design of dsRNA for specific targeting of mRNA that contain nucleotide polymorphisms. Holen et al. specifically teach investigation of the tolerance of the RNAi system for mismatches in the siRNA relative

to the mRNA target is extremely valuable because "[l]ow or no tolerance for mismatches would make siRNAs a valuable tool for allele-specific degradation of the aberrant mRNA in various dominant negative disorders resulting from single base pair mutations." (See page 1763).

Finally, one would have a reasonable expectation of success because Holen et al. teach making dsRNAs with one or two mismatches relative to a target nucleic acid sequence and teach RNA interference using said dsRNA.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Response to Applicant's Arguments

Claim Rejections - 35 USC § 112

The rejection of record of claims 11-23, 25-27, 29 and 31-33 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in response to claim amendments filed 07/12/2006.

Re: Claim Rejections - 35 USC § 102

The rejection of record of claims 11-16 and 21-23 under 35 U.S.C. 102(b) as being anticipated by Crooke et al. (cited on PTO Form 892 filed 01/12/2006) is maintained.

Applicant's arguments filed 07/12/2006 have been fully considered but they are not persuasive. Applicants argue, "Crooke et al. does not teach a polynucleotide containing a repeating pattern of a plurality of modified groups and flanking groups and therefore does not teach each and every limitation of the claims."

Instant claim 11 is drawn to a ribonucleic acid molecule comprising a double stranded structure having a first and second strand wherein said first strand and/or said second strand comprises a pattern of a plurality of groups of modified nucleotides wherein each nucleotide of each of said groups is modified at the 2' position and wherein said groups are arranged in a repeating pattern and further wherein each group of modified nucleotides is flanked on one or both sides by a flanking group of nucleotides wherein the flanking groups of nucleotides in either an unmodified nucleotide or a nucleotide having a different modification than the nucleotides in the modified groups. The specification discloses the modified or differently modified nucleotides may be repeated one or more times and this is a pattern of modification (see page 23, lines 9-14). The specification further discloses a group may actually comprise as little as a single nucleotide (se page 23, lines 15-17).

First, the instant claims do not require a repeating pattern of a plurality of modified groups *and* a repeating pattern of flanking groups. The instant claims only require the double stranded structure have a plurality of 2'-position modified groups in a repeating pattern and further wherein each 2'-position modified group is flanked on one or both sides by a flanking group wherein the flanking group comprises unmodified or differently modified nucleotides. Secondly, the limitation of the flanking groups on one

or both sides of a 2'-position modified group is interpreted to mean each 2'-position modified group in a pattern can be separated by one flanking group and that flanking group would therefore flank each 2'-positon modified group on one side. Thus, the dsRNA molecule taught by Crooke et al. comprises 2'-methoxy modified nucleotides on either side of an eight base ribonucleotide group (see column 50). Each group of 2'-methoxy modified nucleotides is repeated once in the dsRNA and therefore would form a pattern. Further Crooke et al. teach an eight-base ribonucleotide group flank each group of 2' -methoxy modified nucleotides on one side. Crooke et al. teach the pattern of modification is the same on both the sense and antisense strands and therefore the pattern of modification on the sense strand aligns with the pattern of modification on the antisense strand.

Thus, Crooke et al. anticipates claims 11-16 and 21-23 of the instant application.

The rejection of record of claims 11-19, 21-23, 25-27, 29 and 31-33 under 35 U.S.C. 102(e) as being anticipated by McSwiggen et al. (cited on PTO Form 892 filed 01/12/2006) is maintained.

Applicant's arguments filed 07/12/2006 have been fully considered but they are not persuasive. Applicants argue McSwiggen et al. does not disclose any pattern of modified nucleotides and "...no person of ordinary skill would be able to discern anything resembling a pattern of 2' modified nucleotides in McSwiggen[']s siRNA molecules."

Instant claim 11 is drawn to a ribonucleic acid molecule comprising a double stranded structure having a first and second strand wherein said first strand and/or said second strand comprises a pattern of a plurality of groups of modified nucleotides wherein each nucleotide of each of said groups is modified at the 2' position and wherein said groups are arranged in a repeating pattern and further wherein each group of modified nucleotides is flanked on one or both sides by a flanking group of nucleotides wherein the flanking groups of nucleotides in either an unmodified nucleotide or a nucleotide having a different modification than the nucleotides in the modified groups. The specification discloses the modified or differently modified nucleotides may be repeated one or more times and this is a pattern of modification (see page 23, lines 9-14). The specification further discloses a group may actually comprise as little as a single nucleotide (se page 23, lines 15-17).

As stated in the Office action filed 1/12/2006, McSwiggen et al. teach, in Figure 5, a double stranded structure comprising a first strand and second strand wherein the first and second strand comprises groups of modified nucleotides at the 2' position. Specifically, SEQ ID NO. 665 comprises a nucleotide sequence of a sense strand comprising nucleotides "cAuGGcuGccAucuGCGccTT" wherein the lower case nucleotides are 2'-O-Methyl modified nucleotides and the upper case are unmodified nucleotides. The above recited sequence comprises a plurality of groups of modified nucleotides at the 2' position wherein the modified groups are flanked by unmodified nucleotides. Further, the above recited sequence comprises a 2'-position modified group that is repeated at least once forming a pattern wherein the pattern is, starting

from the 5' end: two 2'-position modified nucleotides i.e. groups, wherein this pattern of modified groups is flanked by an unmodified nucleotide on one side. This pattern is repeated at least five times in the sequence as designated herein by bolded nucleotides: "**cA**uGGc**uG**c**cA**uc**uG**CGc**cTT**". Further this pattern, two 2'-position modified nucleotides flanked by an unmodified nucleotide on one side, is the same on the antisense strand of the double stranded structure. McSwiggen et al. teach in Figure 5B, the pattern of modification on the first strand is shifted by one nucleotide relative to the pattern of modification on the second strand.

Thus, McSwiggen et al. anticipates claims 11-19, 21-23, 25-27, 29 and 31-33 of the instant application.

The rejection of record of claims 11-19, 25-27, 29 and 31-32 under 35 U.S.C. 102(b) as being anticipated by Agrawal et al. (WO 94/01550) is withdrawn in response to Applicants arguments filed 07/12/2006.

The rejection of record of claims 11-20, 29 and 31-33 are rejected under 35 U.S.C. 102(e) as being anticipated by Tuschl et al. (WO 02/44321) is withdrawn in response to Applicants arguments filed 07/12/2006.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached at 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Kimberly Chong
Examiner
Art Unit 1635